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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,858	03/14/2002	Bonnie M. Davis	U 013913-4	4479

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/099,858	DAVIS, BONNIE M.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-40* is/are pending in the application.

4a) Of the above claim(s) *5-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/10/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

Applicant's arguments over the 35 USC 112 first paragraph rejection have been considered and are not found persuasive. Applicant first states that support for the amendment of "...other than one diagnosed as suffering from Alzheimer's disease..." was addressed in the "previous action" and was not addressed by the examiner. This claim limitation was amended on 1/13/2006 and the next action after that was a restriction requirement (after filing an RCE) and then the Non-final rejection on 1/4/2007. Therefore, this issue has not been addressed in any prior actions. Applicant's argue that support for the amendment is found in paragraph 8 of the specification in which it is reported that galanthamine is used for the treatment of Alzheimer's disease. This argument is not persuasive because nowhere in the specification is there a specific teaching of treating patients that have not been diagnosed with Alzheimer's disease. A statement that galanthamine is used for the treatment of Alzheimer's disease does not read on the claim limitation of "....other than one diagnosed as suffering from Alzheimer's disease". Therefore the 35 USC 112 first paragraph rejection is maintained.

Applicants argue that there is no distinction between different types of nicotinic stimulation in the second 35 USC 112 first paragraph rejection. Applicants argue that allosteric potentiation is one way of providing nicotinic stimulation but that the applicant should not be required to limit the claims to one particular means for implementing the invention when one in the art would recognize alternative ways of effecting similar

means. This argument is not persuasive because as was pointed out in the rejection, there is not sufficient evidence to support the claimed treatment with all nicotinic allosteric potentiators or nicotinic agonists. Further, the applicant's election of species of galanthamine as the nicotinic receptor modulator is supported by the specification. Though there may be similar ways of effecting similar means, nicotinic agonists were not art recognized as treating Alzheimer's disease as the time of the invention as discussed by Messer (Curr Topics Med Chem, 2002, 2, 353-358). Messer discusses that the clinical utility of cholinergic agonists has been limited due to unwanted side-effects or a lack of efficacy (see Summary). Therefore, the specification is only enabled for nicotinic allosteric potentiators or acetylcholinesterase inhibitors such as galanthamine. Therefore, the 35 USC 112 first paragraph rejection is being maintained and because of applicant's amendments is modified.

Applicant's amended claim 1 in reference to the 35 USC 112 second paragraph rejection. However, Applicant's did not argue or amend claim 37 and therefore, the rejection is maintained over claim 37.

Applicant's arguments that the claims exclude treatment of patients who have been diagnosed as suffering from Alzheimer's disease in regards to the 35 USC 103 rejection have been considered but are not persuasive. As discussed above, this limitation added into the claim is new matter as there is no discussion in the specification excluding treatment from those patients with Alzheimer's disease. Applicant's also state that the rejection is predicated on the idea that those who suffer from Alzheimer's may also take statins and on the now no-longer accepted idea that

taking statins may reduce the risk of Alzheimer's disease, and that this is no longer relevant to the claims as amended. In response to this argument, the claims were examined as they read on the state of the art at the time of the invention.

Applicant argues that Kivipolto teaches a correlation between elevated cholesterol levels (no distinction made between total cholesterol and low LDL-cholesterol) and Alzheimer's disease and there would be no motivation to administer an Alzheimer's drug to patients with low cholesterol values. However, this rejection was not examined alone but was combined with other references to arrive at the present teaching. Therefore, it was not suggested by the Examiner that there is motivation to administer an Alzheimer's drug to patients with cholesterol values. Applicants further argue that lowering cholesterol, which occurred between the baseline and the demented state could equally well have contributed to the development of AD. This argument is not persuasive because Kivipolto points out (table 2) that high serum cholesterol concentration in midlife was a significant risk for AD later in life compared to controls. Applicants arguments over Table 3 of the Kivipolto reference, which shows the relation of medical history and vascular characteristics to AD, that the data do not indicate that cholesterol-lowering has no preventive effect on the development of AD is not persuasive. The direct comparison of patients receiving cholesterol lowering treatments was only done at re-examination. Therefore, the data is merely teaching that of the 218 people receiving cholesterol lowering therapy, there is a lower incidence of patients having AD.

Applicant's over the Simons reference in that there would be no reason to administer an Alzheimer's drug to patients having low LDL-cholesterol is not persuasive because Simons states that there is a decreased prevalence of AD associated with the use of statins to treat hypercholesterolemia. It is common knowledge within the art that statins are used for lowering LDL-cholesterol levels, therefore, it would be obvious that the treatment of hypercholesterolemia is concerned with LDL cholesterol. Further, the references cited in the Simons reference were art recognized at the time of the invention. Any studies disproving the studies after the time of the present invention are not taken into consideration. Furthermore, the teachings of the references (Jick et al. and Wolzin) support the statement made by Simons because Jick et al. conclude from their studies that a possible explanation for the reduction in risk for dementia may be that the statins reduce the risk (see paragraph 3 on page 1629). Applicant's submitted Wolzin et al. and argue that the non-statin drugs used in the study are used as anti-hypertensives and hypertensives are at risk for AD. Applicants argue that the comparison group is enriched for patients with an elevated dementia risk and the differences between the comparison group and statin users may reflect the underlying diseases rather than the treatments. Wolzin et al. explains that the study was set up to include those with hypertension and cardiovascular disease because one would expect similar age-related prevalence of diagnosed AD in the same patients. Therefore, Wolzin et al.'s results that statins decreased the prevalence of AD compared to age-related patients taking other drugs strengthens their argument that statins have an effect in lowering the incidence of AD.

Applicant's remarks over the Zhou et al. and Burns et al. reviews and Winblad et al. have not been considered because those references are dated in 2007 and 2006 respectively, which is after the effective date of this application.

Applicants make the statement that just because two treatments may be effective against a particular condition does not make it obvious to combine them to treat that condition. This argument is not found persuasive because it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 626 F.2d 846, 205 USPQ 1069, 1072 (CCPA 1980).

Due to Applicant's amendments to the claims, the following modified rejections are being made.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, and 37-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Amendment to the claims in

which it is stated "...other than one diagnosed as suffering from Alzheimer's disease...." is not supported in the specification and is considered new matter.

Claims 1, 3-4 and 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of the cognitive dysfunction Alzheimer's disease of a patient associated with low LDL-cholesterol values (claims 1, 3-4 and 38) with galanthamine, does not reasonably provide enablement for treating all cognitive dysfunctions or all neuromuscular dysfunctions associated with low LDL-cholesterol values with all nicotinic allosteric potentiators or nicotinic agonists. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The nature of the invention and breadth of the claims: The rejected claims 1, 3-4 and 37-40 are drawn to a method for treating cognitive dysfunction (claims 1, 3-4, 38-40) of a patient associated with low LDL-cholesterol values in serum by modulating nicotinic receptors comprising administration of a nicotinic allosteric potentiator or a nicotinic agonist or a mixture thereof and to a method for treating neuromuscular dysfunction (claims 37 and 39) caused by low LDL-cholesterol values in the brain by modulating nicotinic receptors by administration of a nicotinic allosteric potentiators, a nicotinic agonist or a mixture thereof. The claims are considered very broad because the claims are directed to method for treating any cognitive dysfunction or any neuromuscular dysfunction caused by low LDL-cholesterol values in the brain, without specifying which dysfunction is being treated.

(2) The state of the prior art: The state of the art regarding treating cognitive dysfunction and neuromuscular dysfunction caused by low LDL-cholesterol in the brain by modulating nicotinic receptors by administration of nicotinic allosteric potentiators, acetylcholinesterase inhibitors, or nicotinic agonists is not well described, for example see Messer (Curr Topics Med Chem, 2002, 2, 353-358). Messer teaches that the clinical utility of cholinergic agonists in the treatment of AD has been limited due to side effects or lack of efficacy (see Summary). Further, there is no description in the art that all nicotinic allosteric potentiators will treat cognitive or neuromuscular dysfunctions.

(3) The relative skill of those in the art: The relative skill of those in the art is high.

(4) The amount of guidance or direction presented and the presence or absence of working examples: In the instant case, the specification discusses the use of nicotinic modulators to be used in the present invention without actual instruction. Applicants discuss the usage of galanthamine in Alzheimer's disease, which is art recognized. However, Applicant's give a limited discussion of compounds suitable for the invention and give no working examples proving their actual effects on all cognitive or neuromuscular dysfunctions. The specification provides no working examples of treating all cognitive impairments or all neuromuscular dysfunctions caused by low brain LDL by modulating nicotinic receptors by administration of nicotinic allosteric potentiators, acetylcholinesterase inhibitors, or nicotine agonists. Note that lack of a working example is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP § 2164.

(5) The quantitation of experimentation necessary: As stated above, the rejected claims 1, 3-4 and 37-40 are drawn to a method for treating cognitive or neuromuscular dysfunction of a patient associated with low LDL-cholesterol values in serum by administration of an effective amount of a nicotinic allosteric potentiator or a nicotinic agonist. The specification provides no working examples that all nicotinic allosteric potentiators or nicotinic agonists will effectively treat all cognitive or neuromuscular dysfunctions. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return

for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-4 and 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 37, the recitation of "treating neuromuscular dysfunction resulting from the use of HMG-CoA reductase inhibitors..." render the claims ambiguous. It is not clear as to what dysfunctions the Applicant is referring to. The specification fails to describe the metes and bounds of these claims, accordingly clarification is needed.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-4 and 37-40 rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (U.S. Patent #4,663,318) in view of Kivipelto (BMJ (2001) 322: 1447-1451) and Simons et al. (Neurology (2001) 57: 1089-1093).

Davis et al. teach that galanthamine is useful for the treatment of Alzheimer's disease (see whole document).

Davis et al. do not specifically teach that the patient population receiving the treatment is associated with low LDL-cholesterol values or that the low cholesterol values are a result of treatment with HMG-CoA reductase inhibitors.

Kivipelto et al. teaches that high serum cholesterol increases the risk of Alzheimer's disease (pg. 1449, first paragraph and Table 2).

Simons et al. teach that there is a decreased prevalence of Alzheimer's disease associated with the use of statins (pg. 1091, paragraph 2). It is taught that statins cross the blood-brain barrier and decrease de novo cholesterol synthesis by inhibiting HMG-CoA reductase (pg. 1091, paragraph 2).

It would be obvious to one having ordinary skill in the art at the time of the invention to add to the drug regimen of an elderly patient that suffers from a cognitive disorder and is taking statins for hypercholesteremia, an effective amount of galanthamine to improve cognitive behavior because Davis teaches that galanthamine is effective in treating Alzheimer's disease, which is a disease of cognitive impairment. One would have been motivated to do so because the prior art teaches that high levels of cholesterol and Alzheimer's disease are related (as taught by Kivipelto), and that patients receiving statins for hypercholesteremia have a lower incidence of Alzheimer's disease (as taught by Simons); therefore, one would have a reasonable expectation of success with treatment of galanthamine for a cognitive disorder.

Furthermore, Applicant has not provided any evidence showing the criticality of cholesterol levels at 109 mg/dl. Accordingly, identifying suitable patients by observing their cholesterol levels during hypercholesteremia treatment would be achieved by routine experimentation.

Conclusion

No claims are allowed.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is 571-272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER